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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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and

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PRESIDENTIAL ADDRESS

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

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INAUGURAL ADDRESS*

GEORGE BAEHR

President, The New York Academy of Medicine

DURING the year which has just ended, the Academy has sustained an irreparable loss in the death of its late President, William Worthington Herrick. During his brief incumbency of office, the general fellowship, unfortunately, had too little opportunity to appreciate his significant services to our Academy. Those of us who were privileged to serve as Trustees and members of the Council under his wise leadership soon learned to rely upon his calm judgment and to look hopefully to the future of the Academy under his strong and able guidance. It is with a feeling of sadness and deep humility that I undertake the burdens which he has relinquished.

Because of the scientific program scheduled for this evening's meeting, time is not available in which to report to you on behalf of the Trustees and Council concerning the activities of the Standing and Special Committees and of the various Sections of the Academy during the past twelve months. Annual reports dealing with most of these activities will be published shortly. I urge you to read these reports if you are to appreciate the ever-broadening influence of the Academy

* Delivered January 3, 1946 at the Annual Meeting of The New York Academy of Medicine.

and of its fellowship in the fields of public health, medical education and of clinical and scientific research.

I am pleased to be able to report to you that the Academy has weathered the financial and other difficulties of the war period without a break in any of its basic functions. Due to generous financial assistance from some of our fellows and, above all, from members of the Lay Advisory Council under the Chairmanship of Mr. Walter Gifford, our financial position has actually been strengthened and, in spite of mounting costs, the year 1945 has ended without an operating deficit. A substantial share of the credit for the stability of the Academy during these difficult years of the war belongs to the Director, Dr. Herbert B. Wilcox who, I am sorry to inform you, has announced his retirement on October 1st. Another large share of the credit goes to our well named Steering Committee under the Chairmanship of Dr. Harold Mixsell.

The financial picture for the current year however is somewhat different. In spite of painful economies, the annual outlay for salaries has of necessity increased 35 per cent since 1940, other operating costs more than 20 per cent. Repairs which could not be undertaken during the four years of war can no longer be postponed. Personnel shortages which were tolerated by the Fellows and visitors to the Academy and its Library because of the war, now require prompt adjustment. Our Finance Committee, therefore, estimates that income from annual dues and from endowments this year will fall short of meeting our minimum budget by $38,500. However, I am sure that we can continue to depend on Dr. Mixsell's Committee and upon other Fellows and lay friends of the Academy to help us bridge the gap that lies ahead.

Three non-recurring items must also be met before the immediate needs of the Academy can be fully realized:

1. A sum of $35,000 is required for the purchase of foreign books and periodicals for the Library which could not be secured during the six-year period of hostilities but which our agents overseas have been assembling for us during the war years.

2. Dr. Mixsell's Steering Committee has collected $300,000 for an addition to the Library, which is most urgently needed in order to provide additional stack space for the books which now fill all available shelves and overflow on to the floors and the cellar of the building and of several adjacent tenement houses belonging to the Academy. Of this sum, about $190,000 has come from the pharmaceutical industry,

as an expression of its appreciation of the importance of the Library for scientific and industrial research. I am privileged, tonight, to announce gifts totalling another $110,000 for this purpose from the Commonwealth Fund, from Mrs. Henry L. Doherty, and from the late Dr. Sara Welt Kakels. For these generous gifts, the Academy is deeply grateful. The goal has almost been reached, leaving a balance of only $50,000 which is still needed to complete the amount required for construction of the building and for equipment.

It is regrettable that times does not permit more than brief mention of the efforts of the Academy to meet the overwhelming demands of returning medical officers for retraining in medicine. Almost one-fifth of all the grade A interneships and residencies of this country are to be found in the hospitals of New York City. It was, therefore, to be anticipated that thousands of young physicians who had been taken into the military services after an accelerated medical school curriculum and a most abbreviated and inadequate interneship should, upon demobilization, look to this City and to The New York Academy of Medicine for placement in hospital residencies, rather than for so-called "refresher" courses. Through its Committee on Medical Education, the Academy has served as a clearing house for the hospitals of the City. Many discharged medical officers have been provided with opportunities for training in medicine, surgery and the various specialties. But the flood of applicants has been overwhelming and the total picture, it must be confessed, has not been satisfactory. Much more must be accomplished in persuading the hospitals of the City to increase the number of their interneships and residencies, cost what it may, and to reorganize them in such a manner as to make them a real educational experience.

Most of tht 60,000 medical officers in the Armed Forces are young men. While all over this Nation, people debate the merits of new methods for the distribution and payment for medical care, by far the most important problem in this field lies right before us. We are confronted with a "lost generation" of young physicians, who plead for some help before they are forced to return to the private practice of medicine. Their neglect at this time will profoundly affect the quality of medical care in this country for several decades. Above all other responsibilities during the next few years, the Academy will dedicate itself to a solution of its full share of this vital problem.

The primary aims and purposes of the Academy are the advancement of public health and medical care through education and research. In the spirit of its tradition of public service over a period of almost one hundred years, it would be impossible for the Academy to stand aloof from the postwar problems of medical care which are now troubling the people of this country. I shall, therefore, take the liberty of devoting the remainder of this discourse to a statement prepared by the Academy's Committee on Medicine and the Changing Order, of which Dr. Malcolm Goodridge is Chairman. This statement, which I shall read verbatim, has been approved by the Council of the Academy.

During the past three years, The New York Academy of Medicine, through its Committee on Medicine and the Changing Order, has been making an intensive study of current social and economic changes and of their effects on medical care and public health. This Committee was appointed to study all problems involved in the distribution of adequate medical care, embracing not only the immediate management of the sick, but also preventive medicine, public health, medical education and research, nursing, hospitals, convalescent care and rehabilitation, dental care, health education of the lay public, and finally the ways and means to meet the costs of such services. The Committee on Medicine and the Changing Order is not, in the strict sense of the term, a medical committee, nor does it represent solely the medical profession. It includes in its membership a large percentage of non-medical persons, representing labor, industry, law, social work, the clergy, and the public at large, who have had full opportunity to participate in the work of the Committee and to express their points of view. The Committee has met weekly and, at times, more often, to listen to the testimonies presented by invited experts. It has spent many hours in deliberation, collectively and in subcommittee meetings at which smaller groups of experts have studied and dealt with the specific phases of problems confronting present day medicine. The Committee has been supported in its work by a corps of experts, and the costs of its work have been met by grants from The Commonwealth Fund, the Milbank Memorial Fund and the Josiah Macy, Jr. Foundation. In every respect, therefore, the Committee is representative of all the varied and broad interests that are concerned in the problems of the extension and improvement of medical service.

The Committee on Medicine and the Changing Order has not yet

completely formulated the recommendations of its Final Report, which it expects will be published during the current year. However, the Special Message sent to the Congress by President Truman on November 19, 1945, in which he urges the creation of a system of national compulsory medical insurance, as well as other changes in the organization of medical care in the United States, impels The New York Academy of Medicine, through its Committee on Medicine and the Changing Order, to issue a statement at this time.

The New York Academy of Medicine is essentially in accord with the objectives reflected in the President's Message. It is fully cognizant of the many lacks in medical care which now exist in the United States, and which most certainly are in need of urgent remedy. It agrees that the health of the people is a matter of national concern, and that every effort should be made to provide all our people with adequate medical care and the opportunity to achieve and enjoy good health. However, while endorsing President Truman's objectives, the Academy cannot endorse all of the methods he proposes for their attainment.

We are mindful of the great achievements of modern medicine, which have been effected, particularly during the last forty years, under the prevailing system of medical practice. By the side of the many admitted inequities in the distribution of medical care stands the attested fact that the health record of the United States, as witnessed by mortality and morbidity statistics, is today outstanding. No nation of comparable size and complexity, with as many varieties of circumstances under which its people live and work, has attained as much in fostering the health of its citizens as has the United States. Before, therefore, venturing upon untested schemes which involve abrupt, nationwide changes, we must strive to determine whether we could not achieve the objectives which the President has voiced, and which we share, more quickly and more effectively by procedures that are, in our opinion, less hazardous.

The President's Message advances five specific recommendations. With the first of these, advocating the construction of hospitals and related facilities, the Committee on Medicine and the Changing Order is substantially in accord. In many rural areas and even in suburbs of large cities there is a serious shortage of hospital and clinical facilities. This problem, however, will not be solved by the simple procedure of erecting structures and creating physical facilities; for, to be effective,

hospital and health centers must be adequately staffed with competent personnel. At the present time there is not available, and the immediate future does not promise to provide, a large enough body of trained and experienced medical and other personnel to warrant a rapid expansion of hospital facilities. We are currently confronted with the distressing example of the grossly inferior hospitalization and medical care provided for our veterans. As in every other effort to extend and improve medical facilities, we are compelled to recognize the numerous interrelated factors—physical facilities, economic resources, medical education and training, and public education—each of which has a profound bearing upon the other, and all of which, collectively, are essential to the expansion and improvement of the medical services.

The President's second recommendation proposes an expansion of public health, maternal and child health services. This, too, the Committee endorses in principle, with the caution, however, that experimentation is needed to avoid the sacrifice of valuable facilities and procedures which are already functioning. We are not here venturing into virgin territory. Public health, as well as maternal and child health, have been the concern of the American public and of American government for many decades, and particularly during the last forty years. We already have many excellent facilities, some run by state and local official organizations, others by voluntary and professional groups. Whatever expansions are undertaken should be developed in relation to these existing facilities.

The President's third proposal, to advance and support medical education and research, the Committee on Medicine and the Changing Order also endorses in principle. Here, too, however, governmental aid to medical education and research should be of such character that it fosters and supports, but does not direct and dominate. The Academy, through its Committee on Public Health Relations, has already taken its stand on these matters in a resolution endorsing, with some slight modification, the Magnuson Bill now before the Congress.

The President's fifth recommendation, that means should be devised for protecting workers against loss of wages resulting from sickness and disability, the Committee endorses without reservation.

There remains to be considered the fourth of the President's recommendations, namely, national compulsory medical insurance. To this recommendation the Academy is definitely opposed. As a result of the

studies of its Committee on Medicine and the Changing Order, the Academy is convinced that any scheme of national compulsory medical insurance at this time would lead to most unfortunate results affecting the health of the public, and the science as well as the practice of medicine.

It is not possible, under the circumstances, to discuss this fourth proposal in the President's Message in any detail. The proposed scheme of prepayment of medical costs based upon the enactment of compelling legislation and the collection of tax moneys is deceptive in its simplicity. Our studies have shown that the problem of providing for extensions of medical care is far from simple; indeed it is extremely complex, for it involves not only readjustments in the care of the sick but also, among other factors, the structure and content of medical education and the broad fields of social, industrial and preventive medicine. Payment for medical care through insurance represents only a fragment of the problem. It should be obvious that insurance cannot do more than spread a portion of the risk of costs. It cannot solve our medical problems, because it cannot create the services essential for improving and extending medical care. It will not of itself teach the public to appreciate or to utilize effectively whatever medical resources are even now available to it. Insurance is most certainly incompetent to raise the quality of medical practice.

On the contrary, there is a wealth of experience which shows that under compulsory medical insurance on a nationwide scale, though a larger number of people receive medical care, the quality of medical services rendered by the individual physician tends to decline.

Under our present forms of rendering medical care, which the President indicates would remain unchanged, the direct payment for medical services by a third party, the insurance fund, introduces a fundamental disturbance in the attitudes of both the subscribers and the doctors. The patient is tempted to demand more attention than he requires. Still more serious is the temptation of the practitioner to add to his income by rendering unnecessary service. Excessive demand, on the one hand, and unnecessary service on the other, inevitably result in superficial performance. The financial rewards for volume of service and the pressure of patients constitute a combination of influences which to many is irresistible. This has been the recent experience in New Zealand and it has been our own experience in the operation of

Workmen's Compensation Insurance.

Unfortunately, the alternative method of payment under an insurance scheme, namely capitation, whereby an annual stipend is paid to the physician for each insured patient on his list, likewise produces objectionable results. When the financial reward is fixed, some physicians are tempted to render as little service as possible.

Experiences abroad and in the United States by no means preclude the success of carefully organized prepayment medical insurance plans in this country. At the present time, however, we in the United States do not know how best to develop such medical insurance. We need a good deal of carefully planned and regulated experimentation. We lack experience not only from the actuarial angle but, what is still more important, from the service angle. We must realize also that we have no basis in our own experience upon which to estimate what the contemplated extensions in medical service are likely to cost. We do know from European experiences that under national compulsory medical insurance, even as the general level of medical practice is lowered, its costs are raised. Furthermore, in the light of our own political history, we must recognize that wherever there are available for distribution large sums of "government money," there also thrive political influence and political patronage.

The Academy's Committee on Medicine and the Changing Order is not concerned with maintaining the "status quo" in medicine. It has devoted several years to exploring new methods for correcting the many deficiencies in medical service. As a result of its studies, it is convinced that the problems involved in the improvement and extension of medical service to all the people of the United States are numerous and diverse; hence, the ways to their possible solution are, and must be, of many kinds. In the opinion of the Committee the expansion of medical services indicated in President Truman's first, second and third recommendations, with the modifications noted, would serve immediately to extend and to improve the quality of medical care rendered to our people, and to lay the foundation upon which a better organization of the medical profession could be achieved.

In opposing the fourth recommendation, calling for immediate nationwide compulsory medical insurance, the Committee maintains that the problem of payment can be solved by methods less menacing to the high standards of medical service which have developed in this country

over the years. To this end it offers a series of inter-related proposals, designed not only to make more medical service available to our people, but also to improve its quality. These proposals are not easily summarized out of their context in the Final Report, but it is possible at least to indicate the diverse paths upon which the Committee believes we must travel if we are to reach an orderly solution of the many problems which today confront us.

The Committee recommends, among other things, that voluntary, nonprofit insurance be given a thorough trial as a means of providing medical services for low-income families through prepayment. At the same time it recognizes that plans of this nature cannot be expected to solve the entire problem, and that in certain instances, for example, when private resources are inadequate, government support, preferably in the form of federal or state grants-in-aid, will be required. The Committee holds further, that it may be desirable to conduct careful experiments at state and local levels with compulsory government insurance, so that we may have in the near future comparative experience with the relative values of voluntary and compulsory procedure.

In order to raise the quality and to round out the scope of medical care extended under any system of payment, the Committee favors not only a number of revisions in medical education, but the gradual extension of group practice. Under this form of practice, which promises far-reaching improvements in the organization of practitioners and specialists, doctors conduct a joint enterprise in medical care in close coöperation with high-grade hospitals, sharing a common plan of remuneration and responsibility for the quality of service they render. The group system is especially attractive to young physicians entering the practice of medicine, who have been accustomed to work together while in training as hospital residents, and who desire to retain their relationship to the hospital, with all its educational and professional advantages. Even those physicians who settle in rural communities should eventually be able, under a well planned system of medical care, to retain or establish such a relationship to a medical center.

It is essential, moreover, that medical group practice units be organized also in relation to teaching hospitals, since an extension of prepaid medical care to all people of low income must inevitably have important repercussions upon medical education and research. The medical schools, for their part, must change their methods if they are to train

doctors for a new form of medical care; and no form of medical care can afford to neglect the advantages to the patient of teaching and research.

Because it is much more economical—not alone in terms of money but in human values—to prevent the occurrence of illness than to cure it, the Committee places special emphasis upon preventive medicine in all forms of practice. To the same end, immediate efforts should be made to provide basic public health services for communities which are now lacking in those services. The Committee insists also that further education and enlightenment are sorely needed by all groups concerned —by government agencies, by the medical profession, by private welfare organizations, and most of all, by the public at large.

What is wanted at this time, therefore, is not an overall national compulsory scheme, but a variety of studies and experiments conducted by smaller units at State and at local levels. In this brief statement, it has not been possible to do more than indicate the nature and variety of State and local programs which, with the help of governmental grants-in-aid, may form the foundation for a Nation-wide extension of comprehensive medical care. Specific recommendations as to how such pilot studies and experiments may be carried out will be contained in the completed Final Report of the Committee on Medicine and the Changing Order.

It is the conviction of the Academy that an evolutionary transformation of medical practice is essential if the benefits of modern medicine, and especially of preventive medical services, are to be made more freely available to the people. It is far better to proceed in a somewhat slower but more orderly manner than to expose the nation to the risks, as yet unmeasurable, which immediate adoption of national compulsory medical insurance would entail.

INTRAVENOUS HISTAMINE IN THE TREATMENT OF MIGRAINE*

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SIR THOMAS LEWIS, in 1926, showed that the reaction to local skin irritation was threefold: (1) Local reaction at the site of the irritant, (2) local release of histamine from damaged cells causing the formation of a wheal in the immediate area—and (3) a further release of free histamine into the circulating blood.

Advances in the study of histamine and its physiological actions indicate that such reactions to cell injury may take place in many organs or tissues with consequent release of histamine in quantities much larger than that derived from small areas of the skin. Furthermore, it is generally believed that certain tissue aggregates or organs, remote from the site of injury, are particularly sensitive to histamine, and respond to its presence, even in minute amounts, by vasodilatation. These have been designated shock organs, characterized by their great vascularity, notably of capillaries, and include skin, liver, spleen, mucous membranes, (respiratory and gastro-intestinal tracts), lungs, endothelium and brain, through the cranial arteries and capillaries, especially external carotid, superficial temporal and occipital as well as middle meningeal and internal maxillary.

The second of Lewis phenomena, local wheal formation following irritation or injury, is a local vasodilatation and can be produced at will by the intradermal injection of histamine, especially in susceptible individuals, while larger amounts injected subcutaneously, cause in remote organs, reactions typical of the reponse in allergy. Similarly, release into the circulation of histamine by any mechanism, traumatic, thermal

* Presented November 20, 1945 before the Joint Meeting of Section of Medicine and the Section of Neurology and Psychiatry of The New York Academy of Medicine and the New York Neurological Society. From the Presbyterian Hospital of the City of Chicago.

(either heat or cold), chemical, circulatory, or allergic, may in individuals over-sensitive to this substance, result in an organ response characterized in the first phase at least by vasodilatation and typical sequelae —notably asthma, urticaria, etc.

Histamine in the circulating blood, regardless of the method of its production, remains for an extremely brief time, being rapidly taken out of the blood stream by the cells of various tissues, especially endothelium, where it causes vasodilatation and the characteristic response of the organ involved. Hence, quantitative determination of this substance in the blood is extremely difficult and unreliable, and few data are at hand regarding the concentration necessary to produce such reaction in sensitive and non-sensitive individuals.

It has been rather generally accepted that the phenomenon of migraine is precipitated by the release of histamine into the blood stream as the result of an allergic reaction and that the major attack of migraine develops only in those individuals whose tolerance to histamine is low and who would be hyperreactors at some one of the phases, as the result of intradermal, subcutaneous or intravenous injection of this substance—(skin test or systemic response).

It has been the contention of many, including the authors, that there are two types of migraine, the vasodilated and the vasoconstricted. This is borne out by well recognized features of both etiology, and treatment of individual attacks. In a relatively high percentage of cases parenteral ergotamine tartrate administered early in the cycle, will ameliorate or terminate the attack, whereas there remain a substantial number who either obtain no relief or experience aggravation of their symptoms from this medication, regardless of giving it early or even anticipating the attack. Obviously the former are in a state of vasodilatation and respond to a vasoconstrictor. Furthermore many of these patients, unresponsive to ergotamine, experience prompt and sometimes lasting relief from vasodilators, particularly nitroglycerine, nitrites and nicotinic acid. Experience with alcohol indicates that many persons are certain to precipitate an attack of migraine with as little as one cocktail (vasodilators) while others obtain definite relief from one or two drinks.

Recently, Atkinson,[1] reporting on twenty-one cases of uncomplicated migraine, found that contrary to his experience in Ménière's disease, he could not divide his patients into two groups by means of the

standardized intradermal histamine response, since he found no hyper-reactors, or as they are generally interpreted, no case of vasodilator mechanism, and that every one exhibited a primary vasoconstrictor mechanism. He and Wolff[2] advance the attractive theory that there may be a dual mechanism in migraine with *primary* localized cerebral vasospasm accounting for localized prodromes or aura, of sensory, motor, ophthalmic, and cortical origin followed by a more generalized vasodilation causing headache, and Atkinson advocates attack on the initial phase with a vasodilator drug (nicotinic acid) with the object of preventing the onset of the headache, rather than waiting for the secondary dilatation to occur and then treating that phase with a potentially dangerous vasoconstrictor.

Atkinson further suggests in his article (Dec. 1944) that such cases might be successfully treated with histamine, and it is on such an investigation, begun in early 1943 that we are reporting. Our preliminary observations on thirty-four cases were reported February, 1945, with two years study of some.

Unfortunately, we cannot accept this excellent hypothesis in its entirety, since many of our objective findings are at variance with such a mechanism. Primarily, many sufferers obtain relief or amelioration of attacks by use of vasoconstrictor drugs *very early* in the attack—with the very first intimation of aura—or even in *anticipation of attacks* which can be predicted because of regularity of cycle, impending menstrual period, dissipation or indulgence in foods known to be harmful. Furthermore the commonly reported experience is that delay in availing ones-self of ergotamine results in diminished or total loss of effect. Thus, in some cases at least, therapeutic effectiveness would indicate *primary vasodilatation* and subsequently either vasoconstriction or loss of response to constrictor therapy. Wolff demonstrated the dilatation of temporal arteries during headache—and experimentally showed that the intensity of the pain was directly related to the amplitude of the pulsation, of the external carotid. Wolff[3] believes and states that pain also derives from sustained contraction of the muscles of the scalp and neck, which contract reflexly from the pain of vascular origin—the muscular spasm per se being painful if continuous, and is of the opinion that failure to obtain relief after ergotamine has contracted the dilated vessels is due to persistence of the contractions of the muscles.

To further study this aspect of the mechanism, we have instituted

scrupulous study of the retinal vessels in order to ascertain if any *reflection* of the state of the cerebral vesels (carotid and branches) can be determined. With the coöperation of members of the department of Ophthalmology, we have studied eye grounds during intervals between the attacks, and when possible persuade patients to present themselves to us, in the hospital or offices, at the first premonition of an attack. Careful observations with accurate notes upon the state of retinal vessels, are carried out at frequent intervals, in some instances without therapy—in others with our various therapeutic agents. Frequently with administration of intravenous histamine, typical headache of great severity will result, necessitating decreasing the rate of flow or its discontinuance, during which times frequent examinations of eye grounds can be carried out, observing the state of the vessels during prodromal stages, at height of attack, and when relieved by nicotinic acid or ascorbic acid.

Results showed no single case in which there was vasodilatation of the retinal vessels even when there was flushing of the skin due to intravenous histamine injection. A large proportion of the cases showed no observable change in the diameter or state of the vessels. However, a few cases showed very definite, and in some instances, marked vasoconstriction of the arteries and arterioles of the retina, intermittent in character, and involving all areas of the retina visible to us. These patients were not hypertensive and examinations between attacks of migraine without therapy showed normal eye-grounds with no such contractions.

It would appear that the contention that histamine vasodilatation involves chiefly the branches of the external carotid artery, is correct. However, vasoconstriction observed in these few cases did indicate that at times the widespread vasoconstriction postulated in migraine may involve the ophthalmic branch of the internal carotid.

Our interest in the problem of treatment of migraine with histamine dates from the work of Shelden and Horton[4] on the successful treatment of Ménière's disease with, first subcutaneous, and later intravenous histamine injections, Horton's recognition and successful treatment of histamine cephalgia,[5] and during the early stages of our work we were greatly stimulated by two articles which appeared at approximately the same time. Miles Atkinson,[6] in May, 1943, discussed the similarity of migraine and Ménière's syndrome, and their relation to

allergy and histamine production, while in July, Rainey[7] described a number of cases of Ménière's which were unsuccessfully treated with subcutaneous injections of histamine, but were greatly benefited by its prolonged intravenous administration.

Rainey's conclusions verified our reasoning. As previously stated, histamine remains in the circulatory blood only momentarily, being taken up rapidly by the cells, in which it is normally found.

Much confusion of thought exists regarding the mechanism of histamine therapy, especially with reference to the term "desensitization," which in this context is ambiguous and leads to erroneous concepts. Consequently we believe the term "desensitization" should be restricted to conditions of true allergy, or the anaphylactic status, in which antibodies exist as the result of previous exposure or reaction to an antigen, by whatever route, with the response to subsequent exposures characteristic to the shock organ or organs involved—(asthma, hay fever, urticaria, etc.).

While not allergists, we believe, as do immunologists, that an antigen must first, be protein in character, and secondly, consist of an aggregate above a somewhat loosely demarcated zone in the scale of protein degradation. Thus, albumin, globulin, and albumoses with relatively enormous molecules, are antigenic, with great immunological specificity, while ascending from the low end of the scale, amino acids, and peptone are non-specific and non-antigenic. They may be injected or absorbed through various channels without production of antibodies and without resulting anaphylactic reactions. Somewhere in the polypeptid range, this specific antigenic property makes its debut, and becomes increasingly potent and specific as each protein molecule assumes its characteristic configuration.

With these facts in mind, we can neither assume that histamine, which is decarboxylated histidine (an amino acid) could produce a state of sensitization or allergy, nor that its parenteral administration can desensitize in the accepted meaning of the word.

Therefore, we must conclude that these individuals are not sensitized, but exhibit degrees of lowered tolerance to histamine, and that successful therapy results from the production of an increased tolerance, either physiological as in the case of alcohol, tobacco, caffein and numerous drugs, or quite probably from the increased production of histaminase, which does not prevent the formation and release of hista-

mine, but is mobilized and available to neutralize or destroy that substance. Keeping further in mind the rapidity with which histamine disappears from the blood, it becomes clear why its long-continued administration intravenously, to the limit of the patient's capacity, often for a period of six to ten hours, will be more effective in creating an increased tolerance than repeated injections which result only in a very brief exposure to its action.

Selection of Cases. We have used no patients in this series who could conceivably have headaches from any other cause, such as sinusitis, neuralgia of the face or scalp, hypertension, infection, skull injury, eye disease, or brain tumor. To date we have accepted patients only with headaches of great severity or those of moderate to great severity. Private cases have constituted the great majority, but a liberal grant of funds for hospitalization and all costs, has allowed us to draw from a large out-patient department those patients whom we considered as pure migraine.

The criteria for selection of migraine are definite but vary in intensity and actual occurrence. All doubtful cases have been rejected in this series. Migraine headaches are paroxysmal, usually unilateral, temporal and post-orbital, and characteristic of the condition is freedom from any symptoms between attacks. Headaches are usually, but not invariably, preceded by aura or prodromes, appearing from six hours or more to within a few minutes of the onset, involving particularly sensory cranial nerves, predominantly vision, hearing or equilibrium, taste and smell, with various cutaneous sensations, and at times objective changes, such as dryness of the skin or a distinctive body odor perceptible to others. Familial history is frequent, and numerous observers report that inheritance of migraine from the paternal side is usually more severe than from the distaff line. Evidence of allergy and of other allergic states such as hay fever, and urticaria is common, and to specific foods, notably chocolate. Freedom from attacks in pregnancy after the first trimester is almost universal. Attacks usually involve nausea and vomiting, or nausea alone.

Migraine equivalents are frequently encountered either as a complete change in pattern of the attack, or as totally unrelated to sick headaches. Post, and one of the authors (W. A. T.) in 1924 recognized that paroxysmal tachycardia was in practically all cases a migraine equivalent, or cardiac migraine, and collected nearly fifty cases in which

the tachycardia entirely replaced the typical headache, alternated, or for longer or shorter periods replaced one another. Vaso-vagal attacks (Gowers' Borderland of Epilepsy) are largely constituted of prodromes or aura which fail to materialize as a full blown attack.

Determination of specific food allergies by elimination diets is made difficult by a refractory period, such that, after partaking of food known definitely to produce an attack, the patient may thereafter for a period of from two to eight or ten days, further indulge without ill effect. In our experience, skin tests for foods have been largely unsatisfactory, either as positive or negative criteria. The remarkable variation in the results of skin tests for food parallels the unreliability of interpreting the results of *histamine skin tests* and in our experience both of these methods of investigation may be largely discarded.

Treatment

All patients have been treated by the intravenous injection of 1 mg. of histamine base as histamine acid phosphate diluted in 500 cc. of isotonic sodium chloride solution. Initially, three injections were given on alternate days. Later four injections, and at present, five or more such treatments usually on successive days are given. Injections are given very slowly, about five drops per minute, at the beginning, and the rate increased or modified according to the individual response, the entire procedure taking from three to eight or more hours. When possible the rate is increased to thirty or even forty drops per minute, in which case three to four hours will suffice. Blood pressure is taken every half hour, and any decided drop is considered an indication for reduction of the rate or termination of that treatment, usually temporarily. Too rapid an injection will result first in flushing of the face, later the chest and shoulders, often tachycardia, and finally a typical headache, mild to severe, which may be relieved by slowing the rate, or by injection, directly into the tubing, or otherwise, of epinephrine or ascorbic acid (1,000 mg.). The onset of urticaria or asthma is an indication for similar procedures.

Gastric analysis, done in most of the recent cases, shows a very high acidity with a high amount of secretion, as compared with fasting or control aspirations. With half hour aspirations or continuous aspirations, the patients experience no distress, otherwise many complain of heartburn. which is relieved by alkaline powder, or prevented by routine

Table I—Criteria for Selection of Cases of Migraine

They Are:

Paroxysmal
Usually unilateral—post orbital, supraorbital or occasionally occipital

The Patient Is:

Free of symptoms between attacks
Free of symptoms during second and third trimesters of pregnancy
Frequently allergic

The Aura:

May involve all sensory cranial nerves, especially
II Scotomata, blindness, diplopia, hemianopsia
VIII Deafness, tinnitus, vertigo, equilibrium
I Smell
Cutaneous sensory, pruritus, subjective changes in temperatures

Equivalents:

Paroxysmal Tachycardia
Vaso-vagal attacks (?)

Table II

Number of Patients	75
Sex—Male	11
Female	64
Average Age	38 years
Average Age at Onset	18 years
Average Duration of Migraine	20 years
Average Length of Attacks	25 hours

(Excluding Cases of Migraine State)

Table III—Relief Obtained

Relief	*Mod. Severe*	*Very Severe*	*Total*
Complete, Permanent	12	18	30
Complete, Temporary	4	7	11
Partial	13	12	25
None	5	4	9
Total	34	41	75

(66 out of 75 experienced relief)

TABLE IV—TYPE OF INJECTION PRODUCING RELIEF

Relief	*Intravenous Most*	*Adjunct Histamine Most*	*Total*
COMPLETE, PERMANENT	27	3	30
COMPLETE, TEMPORARY	9	2	11
PARTIAL	22	3	25
TOTAL	58	8	66

58 patients received intravenous only
16 patients received intravenous plus adjunct histamine

frequent feedings and powder. Two hemorrhages from unsuspected ulcers have prompted us to careful histories and adequate acid control. Precautions must necessarily be taken in the long continued use of a substance having such marked effects on circulation and gastric acid secretion—particularly the danger of thrombosis in event of falling blood pressure and decreased velocity of blood flow. No cases were treated in which hypertension, or cardiac or renal impairment were found to exist, or in which there was evidence of mental or central nervous system disease. Evidence of increasing tolerance was almost universally present, in the rate of flow at which successive doses were tolerated. Many patients were unable to take more than 50-100 cc., usually because of severe headache, at the rate of five drops per minute, on the first treatment, and tolerated progressively larger amounts at a more rapid rate until the entire 500 cc. was taken. Only then was the course of treatment considered started, and four additional doses given.

Seventy-five patients with pure migraine have been treated, with an average age of 38 years (Table II). The average age of onset was 18, and attacks had lasted from 3 to 40 years—an average of 20 years. Not including three cases of status migrainicus, the headaches lasted 25 hours and occurred every 11 days. No patients were used whose attacks were so mild as not to interfere with their daily life or activities. The remaining ones were divided into moderately severe (34), and very severe, the latter group (41) including only those who were incapacitated for more than eighteen hours or whose headaches were so severe as to require opiates for relief.

Evaluation of Results

Evaluation of results has not been arrived at haphazardly, with each of us having possibly different standards or ideals, but from analysis of objective statements by the patients from a follow-up questionnaire sent every three months, with squares in which the current condition may be checked and returned in a stamped self-addressed envelope.

This contains data as to dates of treatment, filled in by us with patient's name and hospital number. They report: My headaches are: *Well–Better–Unchanged–Worse*–with other columns for: *Frequency –Severity–Duration–Nausea and Vomiting–Prodromes.* Data as to relation of relief to treatment: *Hospital Treatment–Later Treatment.* Space below for expression of own opinion regarding success or failure of treatment–of actual attacks, modifications of attacks, aura, etc.

Results: Classification

We have found 4 different types of response as far as relief is concerned.

1. Those whose relief was immediate–complete and apparently permanent (up to 2 years 8 months).

2. Those whose relief was immediate and complete, but whose headaches recurred after weeks or months, and who were subsequently improved or relieved by subcutaneous injections of histamine or by repeating the intravenous program.

3. Those who did not experience immediate relief, after the intravenous treatments, but who gradually obtained complete or satisfactory relief either spontaneously or by later subcutaneous injections of histamine.

4. Those who obtained no relief.

Statistical Results. Seventy-five patients with very severe or severe headaches, indisputably migraine in character, were treated in this manner. Immediate complete relief to this date, covering a period of more than 2½ years, has been obtained in twelve moderately severe and 18 very severe cases. Complete temporary relief in 4 moderately severe and 7 severe cases; partial relief in 13 moderately severe and 12 severe cases; no relief in 5 moderately severe and 4 very severe cases. That is, 66 out of 75 experienced a degree of relief, ranging from partial to total.

Other Results. It is interesting to note that migraine equivalents

respond as do the classical attacks. Two patients with frequent and verified attacks of paroxysmal tachycardia reported complete freedom from such seizures, one permanently to this date, one reporting freedom for two years, with gradual return of infrequent, mild and brief attacks synchronous with the reappearance of an occasional mild but typical migraine. She is anxious to return to the hospital for further treatment.

Unprompted reports of improvement during the two past hay fever seasons have been recorded, as well as some benefit in cases of urticaria and asthma, for which therapy was not instituted as such.

Criteria for Prediction of Successful Therapy. There is no royal road to the solution of this problem. Theoretically the vasodilator cases should respond to histamine therapy, but as Atkinson has shown, they may be few. Our results from histamine skin testing have been of little or no value, and we find ourselves totally unable to predict or promise satisfactory results from information obtained from any other sources, such as character of attacks. The most satisfactory criterion is that of producing a typical attack by the subcutaneous injection of 0.1 mg. of histamine.

Our results have lead to other speculation in interesting and distant fields. What is the role of ascorbic acid in ameliorating the attacks brought on by histamine? The introduction of 1000 mg. into the rubber tubing results in prompt and complete relief from the induced headache, whereas similar therapy seems without value in an established spontaneous attack. Does the use of ascorbic acid either prior to or during histamine treatment nullify to any extent the desired result? The intriguing work of Simon L. Ruskin, demonstrating the enhanced effect of the ascorbic salts of calcium, ephedrine, epinephrine, and benzedrine (drugs which constrict the nasal mucosa), over the effect of other commonly used salts of these drugs in overcoming histamine constriction of the bronchioles, may prove the key to the solution of some problems.

The logical conclusion following results obtained here, would indicate that long-continued intravenous histamine medication, presumably 24 hours at a time with controlled rate of injection up to the patient's point of tolerance, will be even superior to the present shorter method of injection.

This work does not in any manner explain the phenomenon of migraine, and is merely a manipulation for its relief, one step ahead of

giving aspirin pills.

The hereditary, constitution factors that cause these sufferers to exhibit lowered tolerance to histamine may be inherently due to a defect in the mechanism of protein metabolism, or failure to produce histaminase in adequate or rapidly available amounts.

A method of treatment for any malady as common and severe as migraine will unfailingly be used for headaches in its very general aspect, and will result in failures and disappointments. A potentially dangerous drug should therefore be used with great caution on a critically selected group comprised, not of those that could be or probably were migraines, but only of those that had to be—and failures or partial relief, even in these cases were common.

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PSYCHIATRY IN A GENERAL HOSPITAL*

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I was asked to talk on "Psychiatry in a General Hospital" and accepted willingly because I finished last year a ten-year period of developing a Psychiatric Service at the Massachusetts General Hospital. Giving this talk has caused me to pause and contemplate what has been accomplished, and to evaluate successes and failures.

This service has been a success because it was wanted, at first by the Medical Service and later by all the other departments of the hospital to a greater or less extent. The success I believe was possible because we psychiatrists of the staff agreed not to push psychiatry, but to try to show by therapeutic results what we could do. Our slogan was "peaceful penetration without propaganda." The Surgical Service soon called us in and several investigations were made and papers published. With Neurology and Dermatology we also made close association, and since then the other departments have come to us more and more asking for consultations. The tardiness or incompleteness of acceptance of us by any department has been largely a measure of the resistance of the head of that department to psychiatric concepts. Many physicians and most surgeons accept a psychological explanation of symptoms only as a last resort. That is why they usually make a diagnosis of neurosis by ruling out everything else instead of studying the patient as a person and evaluating clinically the presence of socio-psychological factors. This can be done and this is what the psychiatric staff has been patiently trying to teach.

The Staff has varied in number between twenty and thirty psychiatrists, of whom three were full-time with one or two full-time assistants and a resident and intern. The other psychiatrists gave part

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* From the Psychiatric Service of the Massachusetts General Hospital and the Massachusetts Division of the Hall-Mercer Hospital.

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TABLE I—DISCHARGE DIAGNOSES—1941-1944

PSYCHOSES	146
HYSTERIA	99
PSYCHOSOMATIC DISORDERS	86
MIXED PSYCHONEUROSES	77
PSYCHOPATHIC PERSONALITY	64
REACTIVE DEPRESSION	57
ANXIETY STATE	55
NEUROLOGICAL	33
OBSESSIVE-COMPULSIVE	17
EPILEPSY	16
HYPOCHONDRIASIS	10
PHOBIC STATE	8
MISCELLANEOUS	11
Total	674

time for out-patient work or visiting and carried on a practice outside. There were two psychologists and (last not least) three social workers who carried a heavy load in Out Patient and Ward. Much time is spent by the full-time staff in laboratory and clinical investigation. This will not be discussed here; suffice it to say that in the last ten years 75 papers have been published on various subjects. Teaching is also part of everybody's work, for we teach Harvard medical students, nurses, clinical psychologists, social workers and divinity students.

The plant was at first a ward shared with Neurology, where we had 12 beds and only one room for a disturbed patient. In 1941 the new ward was opened in the medical building where we have an 18-bed ward surrounded by medical wards and laboratories. This position in the midst of an active Medical Service is most important. There is no isolation; on the contrary, we meet medical men constantly and everywhere on purpose and by accident. Familiarity has bred mutual appreciation. There are a few exceptions but they are individual and incidental.

The ward is close to our research laboratories. It has 15 beds in an open ward for neurotic men and women and three beds in a small closed ward for disturbed patients. This small ward has a central station for a nurse who can observe all three beds at once. It is protected so that suicide is difficult and is isolated so that noise is not troublesome. There

TABLE II—PSYCHOSOMATIC DISORDERS

NEUROCIRCULATORY ASTHENIA	47
COLITIS	9
ANOREXIA NERVOSA	6
THYROID	5
ASTHMA	3
ARTHRITIS	3
DERMATITIS	3
ULCER OF DUODENUM	2
MISCELLANEOUS	8
Total	86

is a "continuous tub" for sedative hydrotherapy. The open ward for 15 patients has five single rooms and rooms for two or four. There is a large day room in the middle where meals are served at a long table, and where recreation is organized and occupational therapy taught. There is also a small occupational therapy room for noisy crafts. Four single rooms are used as offices for interviewing and there is a large class room for meetings of students, nurses and interns. The proximity of the ward to the research laboratories makes clinical investigation easy. The Out Patient is open five afternoons a week in the Out Patient building, where patients are seen by appointment.

The work accomplished in the last ten years has been in the Psychiatric Ward, in the Out Patient and in the laboratories. In the last four years we have had 674 patients on the Psychiatric Service (see Table I). These may be sharply divided into (a) the psychoses: 146 in number, who were looked after on the small disturbed ward and usually made only a short stay, and (b) the psychoneuroses, who were on the large open ward and stayed from six weeks to three months. These two wards perform different services: the first takes the disturbed patients off the medical and surgical wards and cares for them in isolation with proper nursing; the second is for psychoneurotic and psychosomatic patients who come from the medical wards, from the medical and psychiatric Out-Patient departments, or from outside physicians and members of the staff. This latter group is our main study and it will be seen from the chart that we had more hysterias than any other type of neurosis. Psychosomatic disorders are a close second. The mixed psycho-

TABLE III—PATIENTS ON WARD B8

MEDICAL DISEASE WITH DELIRIUM	64
DRUG PSYCHOSES	52
DEPRESSED	34
SURGICAL DISEASE WITH DELIRIUM	31
SUICIDAL ATTEMPTS	25
EPILEPSY	14
MISCELLANEOUS	12
SCHIZOPHRENIA	11
HYSTERIA	10
NEUROSIS	10
MANIC	3
SYPHILIS	3
Total	269

neuroses also formed a large group and if combined with the anxiety states would make the largest group. They might well have been combined with the anxieties because a great many of the patients whom we label mixed psychoneurosis had presenting symptoms of anxiety attacks with hysterical and phobic symptoms as well. Our main therapeutic effort has been directed towards hysteria, anxiety states and psychosomatic disorders.

The psychosomatic disorders have been divided under various headings, as shown in Table II. First is neurocirculatory asthenia with forty-seven cases, because a special study was made of this disease with Drs. Paul White and M. E. Cohen and patients were brought in from Army hospitals and from outside. This investigation is to be reported shortly in a series of papers. I will only mention here that from the psychiatric standpoint practically all of these patients could have been classified "anxiety state." We have had nine cases of ulcerative colitis on the ward and Dr. Lindemann has seen a great many more in the general hospital and handled them in collaboration with Dr. Chester M. Jones. The other categories are all in small numbers, but that does not mean that we have not seen a lot of each of them in consultation on the medical wards. It signifies that only a few of them have been sent up to the psychiatric ward for treatment. Usually it is a matter of bringing them out of their invalidism on a medical ward and bridging the gap to re-

turning to the outside world by means of the psychiatric ward where patients are up and about and there is active ward regime and much occupational therapy. The psychosomatic disorders are becoming a larger part of our work and this year we have admitted many cases of gastric ulcer and expect to take in more patients with gastrointestinal disease.

Table III gives a list of the patients brought to our small disturbed ward from the other wards of the hospital in the last 21 months. The larger number of these are patients from the medical wards who were suffering from delirium and therefore disturbing their ward. They have usually remained with us a week or ten days and then been returned. Many were not officially admitted to the Psychiatric Service and therefore do not appear on the list of discharged patients. The next largest number are the patients who have become psychotic from drugs. Some of these are acute alcoholics who have been brought into the Emergency Ward and sent up to our ward because of noisiness. There are not many of these because they are usually handled by other institutions. A larger number of drug psychoses are seen in patients who have taken barbiturates in excess or who have had sedatives or narcotics after operation and become delirious. Most of these remain on our ward only a few days and are returned to their own ward or discharged. There are a large number of patients both from the other wards of the hospital and from the Emergency Ward who have become depressed and who are brought over because there seems to be a suicidal risk. Patients from the surgical wards with delirium are usually postoperative and often are those patients in whom it was necessary to use large amounts of morphine to control pain. They make a short stay and recover rapidly if the morphine is stopped and paraldehyde used. The patients who had made suicidal attempts came from the Emergency Ward where they were given first aid and sent to us so that there would be no repetition of the suicidal attempt. These were soon transferred to mental hospitals. Some of our own patients with hysteria or other forms of psychoneurosis had to be transferred from the open ward to the small ward for short periods because of their behavior. It will be seen that this ward, although a small unit has a rapid turn-over and is a great service to the hospital in looking after the disturbed and noisy patients and by watching them effectively with the smallest possible number of nurses. Had these patients remained on their own wards, they would have each

needed three special nurses per day, whereas in a protected ward, three or four patients can be watched by one nurse and a great saving made for the hospital as well as an increase in safety for the patient.

The Out-Patient department is a large, active concern under the immediate direction of Dr. Erich Lindemann. In 1934 there were 475 new patients; the number rose steadily in the next five years to 880. Then with the decline of all departments of the Out Patient, shown in the years 1940-1944, there is a moderate dropping off in numbers, hitting a plateau of 720 new patients per year. The total number of visits makes a parallel curve, the plateau being about 3,200 visits per year. This is about 4½ visits per patient. Since about half of the patients are seen only once as a consultation problem, this means that the average out-patient is seen eight times. Even with this small number of visits we are able to do fairly satisfactory therapy and a large number of the patients report relief.

As to treatment I can make some brief statements. We do not use shock and we do not psychoanalyze patients. Many members of the staff have had psychoanalytical training, but the process of psycho-analysis is too long to use in the ward or out-patient department. Our therapy on the hospital patients can be roughly divided into: (1) *living on the ward* with nursing, social service and occupational therapy regime; (2) all this plus *insight therapy*, which is given by use of interviews with the psychiatrist. In the last ten years we believe that we have learned something about what to do in this interviewing and what to avoid. We try to make the interviews specific and headed toward a definite *limited goal*. After the first two or three talks, one is usually able to decide what these goals shall be. Unless such limitations are imposed, the interviews may degenerate into wandering conversations which scatter over the patient's whole life and which are not much use to the physician or the patient. To use Lindemann's word, we try to reach a solution of the *immediate predicament*. The patient is usually in some sort of a hard situation and this may be used as a starting point. In the light of this, we make up our minds what goal we want to achieve in therapy. We know that it is impossible to lift the whole psychogenic load from a patient's shoulders, but we also believe that it is "the last straw that breaks the camel's back" and that if we remove a few straws the patient may be able to carry the rest of the load. Therefore a limited objective is decided on and this is used as the central point in the inter-

view. For example, with one woman, the objectives were to get her to have false teeth made and wear them and to get back to her job. Having succeeded in these practical aims we had by the way touched on and helped some of her main psychological problems: narcissism, inferiority and ideas of bodily pollution.

If there is no immediate predicament that is easily worked on, one takes the presenting symptom and studies this from the standpoint of *stimulus and response*. One studies what stimulus brings out the symptom and under what circumstances. Bringing up example after example gives material that may bring insight to the patient. We feel strongly that insight must come from the patient and not be supplied by the physician. It is too often the case that telling the patient what is wrong with him psychologically (determined by the psychiatrist's insight) will upset him a great deal, either because the psychiatrist is wrong, or because the patient is not ready for that sort of information.

A very important part of treatment is the *social follow-up* given by the physician and the social workers in the Out-Patient. When the patient leaves the hospital he has made contact with a social worker who will see him in the Out-Patient. This, if properly carried through, gives the patient a feeling of belonging to the group. The hospital with its physicians and social service represent to some extent the family doctor upon whom he can depend and to whom he can return if he needs more help. By this follow-up, especially through social workers, we have helped a great many hysterical patients who at first looked rather hopeless.

In closing I would like to speak particularly about these hysterical patients, our largest single category of patients seen in follow-up. We had thirty-two patients of whom thirty were improved. This is a much higher percentage than is shown in other follow-up studies, so I am skeptical as to its accuracy. Probably the trouble is that in the patients who returned after receiving letters, there is an undue proportion of successes because they wish to return, whereas those who have received no help wish to avoid the doctors and the hospital. Be this as it may, there are a lot of severe hysterics who have improved. The other patients have not improved in as large a percentage.

A large number of hysterical patients had very severe symptoms. These are of the pseudoneurological sort, but there were many with sensory symptoms, pain, headache, and vomiting. We believe in keep-

NAME:

HEREDITY:

Hospital #_____

Date: _____

YEAR	MEDICAL DATA		SOCIAL DATA	AGE
1897				1
1900				4
1902				6
1904	FEARS		MOTHER DIED	8
1906	TANTRUMS "PLEURISY"		FATHER RE-MARRIES	10
1908	HEAD INJURY		" DRINKING	12
1910	APPENDIX OP		ASSAULT	14
1912	HEADACHE, PHOBIA AMNESIAS		M.G.H.	16
1914	ADHESIONS OP			18
1916	FRIGID		MARRIED	20
1918			H. EJAC. PRECOX	22
1920	HEADACHE "HYSTERIA"		SON BORN	24
1922			DAUGHTER BORN	26
1924				28
1926				30
1927	NERVOUS CONVULSION		FATHER DIED	31
1928	PAIN, R.U.Q. D+C		STEPMOTHER IN HOME	32
1929	DYSMENORH. D+C			33
1930	HEADACHE D+C			34
1931	CYSTOSCOPY D+C			35
1932	" D+C			36
1933	D+C			37
1934	" D+C			38
1935	D+C			39
1936	" D+C		SEX URGE +	40
1937	DEPRESSION OBSESSIONS		SON 2 ARTHRITIS ARIZONA	41
1938	ABD. PAIN D+C			42
1939	DUOD ULCER DEPRESSED		M.G.H	43
1940	AGITATED "		"	44
1941			STATE HOSPITAL	45
1942	PAIN, etc.		DAUGHTER'S MISCARRIAGE	46
1943	GALL STONES OP			47
1944			" PREGNANT	48
1945	DEPRESSED		" DIES	49

TABLE IV—LIFE CHART OF PATIENT

ing our diagnosis of hysteria in a narrow range, for those patients who are childish, self-absorbed and full of fantasies and who show amnesias and substitute symptoms for direct action in meeting situations, i.e., make a primary gain by this conversion. (Why it is always called "secondary" I don't know.) We avoid the loose term "anxiety hysteria," which to my mind includes many reactions of the conditioned reflex type and many which are merely exaggerations of normal, physiological responses to emotional stresses. Severe hysterias are common and of those that we saw 90 per cent were in girls between thirteen and thirty. Their paralyses, amnesic stupors, fainting fits, etc., were usually relieved during a stay on the ward, by maneuvering the situation so that they wanted to get well, or by suggestion. We tried to keep them on the ward for only a short period and to return them home as soon as the main symptoms improved. Then a long period of re-education began through the physicians and social workers in the Out-Patient. It was this slow, laborious work of making a lasting friendship with the patient and using it for re-education that eventually brought them out of their hysterical mode of reaction. A surprisingly large number of them returned after five or six years and told us that they were married, had children and were now happy and were having no symptoms. They had grown up and were now acting like adults rather than naive children. This is an important point in hysteria. They must *grow up* so one does not know how much our therapy had to do with improving them and how much it was merely the lapse of years.

On this point it has interested us to look up the past histories of some of the women who have come to us in their involutional period, with the symptoms of depression, obsessions and hypochondriasis. Many of these showed hysterical reactions in their youth and one wonders if this sort of reaction at the age of 50 is not an ordinary fate for the hysterical patient, because we rarely see out-and-out hysterical symptoms after the age of forty and they are much more common under thirty. The life chart of one of these patients (Table IV) shows that she was in the Massachusetts General Hospital in 1912 with hysterical symptoms and was diagnosed hysteria at the age of twenty-four. The events that apparently precipitated her adolescent period of hysteria were the assault and the appendectomy at the age of 14. The operation gave her no relief from pain and led to another operation at the age

of eighteen for "adhesions." She then got along fairly well until her father died and then she had "nervous convulsions" and a syndrome consisting of pain in the right upper quadrant, dysmenorrhea and headache, which recurred once a year for the next nine years and was relieved each time by a dilatation and curettage. Added to this there were four cystoscopies. Nevertheless she went through these years and raised her two children fairly well. Then as her menopause approached she had an increased sex urge, which brought up a lot of anxieties about the sexual assault she had undergone at the age of thirteen, just before the appendectomy. From then on she went into a state of depression, obsession and agitation that at times led her to be hospitalized in a mental hospital. We are much interested in these patients and are collecting a series of them in the hope that we can throw light on the course of untreated hysteria.

The incidence of appendectomy in these hysterical girls is extraordinarily high. Of the 32 hysterical patients listed in this follow-up, twenty had had appendectomies, whereas among 100 student nurses there were only thirteen appendectomies. By keeping our eyes open for thse young hysterics who complain of abdominal pain and are rushed into the Emergency Ward, we have been able to recognize a number of them before operation and in some we have relieved their symptoms by working out their troubles, which are usually adolescent fears related to menstruation and motherhood. Once recognized and with the diagnosis of hysteria in the record, they are much less likely to be operated on. Thus we hope to avoid starting hysterical patients on the operative habit which goes on so disastrously in many of them, as illustrated in the life chart.

I might have spoken about the cases of anxiety neurosis, about the neurocirculatory asthenia patients or about depressions; all are important and interesting but the hysterical patients are the most dramatic. They are difficult patients to work with and bring into play all our patience and skill, yet I am convinced that most of them are helped to an important degree. No follow-up system can prove this because one can always be skeptical and say that the patient would have become well if no therapy had been used. Nevertheless our experience leads me to believe that all the energy, hours and money spent on treating the psychoneurotic patients has been well spent, in terms of human happiness.

BRUCELLOSIS*

Problems of Diagnosis and Treatment

HAROLD J. HARRIS

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THIS second invitation to address the Academy on the subject of brucellosis within 18 months signifies a growing recognition of the importance of this illness. In a lecture given on 19 March 1943 as one of the Friday Afternoon Lecture Series[1] the ground to be covered was essentially the same, i.e., diagnosis and treatment of this ill-understood infectious disease. Much material had to be omitted then because of limitation of time and the wealth of available material. The same handicap exists this evening. I will attempt to avoid extensive repetition but to fill in gaps and to add what seems most important of the new material that has become available.

DIAGNOSIS

The diagnosis of brucellosis cannot be easily established or ruled out. It is one of the most difficult tasks in medicine. Unless one is very wary he may attribute to brucellosis all symptoms which the patient exhibits only to find later that, in addition to Brucella infection, the patient also had a perhaps unrelated psychogenic or somatic illness. One must be constantly on guard against overenthusiasm in making the original diagnosis and against ascribing all symptoms which subsequently arise to the same infection. Conversely, before making a diagnosis of psychoneurosis, one should be sure that brucellosis has been ruled out as a major cause of symptoms. When the neurosis and brucellosis coexist the patient himself often adds to the difficulty of the diagnostic problem by unwillingness to accept the role played by the emotional state.

That brucellosis must be considered in the diagnosis of any obscure illness, including the neuroses, has been said times without number. It has been understatement. Since the disease is common, since it simulates

* Presented 19 October 1944 before the Seventeenth Graduate Fortnight of The New York Academy of Medicine.

a great variety of other illnesses, it seems more sensible to say that its possible existence always should be considered along with tuberculosis, syphilis, malaria, rheumatic fever and the like. Experience has taught me not to wait until all other possibilities are ruled out before thinking of brucellosis but to think of it early. Only in that way can active measures be undertaken to bring about early recovery or cure and to prevent perhaps a lifetime of relapsing acute illness or of continuous or intermittent chronic illness.

Agglutination Test: Having allowed brucellosis the dignity of a place in our thought processes along with the more time-honored illnesses, it is then time to discard the long existent fallacy that all that is necessary is to perform the blood agglutination test—that a "positive" reaction proves brucellosis, that a "negative" one rules it out. Such oversimplification of diagnosis can rarely be successful in other illnesses. It is especially fallacious in brucellosis. The agglutination reaction is negative in the majority of chronic infections and very frequently in the acute illness. It should always be employed, obviously, along with the blood Wassermann, and other routine studies. Its value lies only in a positive finding. Rarely is one misled by a report of agglutination in a titer of 1:80 or higher, although cross agglutination may occur, usually in low titers only.

The report of a negative blood agglutination reaction means just that, i.e. nothing. If the illness is an acute febrile one the agglutination test should be repeated before the intradermal test is done. Agglutinins may appear as the illness progresses but they may be artificially induced by the antigenic reaction of the skin testing material. The report of agglutination in low dilutions of the blood serum only (1:10, 1:20, 1:40) should be viewed with interest and not discarded as unimportant. Another test within a few days to two weeks may show a diagnostically high titer. If not there is usually no reason to defer the intradermal test longer.

Culture: Culture may be undertaken at any time—the earlier the better if one must depend upon it for ultimate proof. Properly done, cultural procedures may require as long as 18 weeks, including adequate study of inoculated guinea pigs. Brucella is among the most difficult of all bacteria to isolate. However, isolation of the organism is the one definitive diagnostic measure. It may be positive when all other tests are negative, as in the classical case of Alice Evans[2] which has been con-

firmed repeatedly. Only the laboratory staffed by capable technicians, who are really interested in the isolation of this organism, should be used for the purpose. Too often routine cultural methods which have virtually no chance of success are employed. Like the agglutination test a negative cultural study is of no significance. The percentage of positive cultures in the presence of active Brucella infection, especially with the abortus strain, is extremely small, even with the most meticulous technique such as outlined by Poston.[3] Culture has the greatest chance of success at the height of the acute febrile illness with the melitensis strain, the least chance in the chronic abortus infection with low grade fever or no fever.

The two other essential tests, the intradermal test and the opsonocytophagic test, should be considered together and done at about the same time for greatest accuracy. If the intradermal test is done far in advance of the determination of the phagocytic power of the white cells, artificial opsonins, along with agglutinins, may be induced.

Intradermal Test: The skin test is best done with 0.1 of a cubic centimeter of undiluted suspension of heat-killed Brucella abortus organisms in a concentration of about 2,000 million organisms per cubic centimeter. Use of a mixed vaccine is likely to result in an unnecessarily severe reaction because of the presence of Brucella suis or Brucella melitensis. The technique and significance are entirely comparable to the intradermal tuberculin test. A positive reaction indicates sensitivity to Brucella protein, acquired through infection. It does not indicate whether or not that infection is still active. The most important early error in interpretation of the cutaneous reaction lay in labelling as negative all those that did not react violently. A skin reaction that becomes apparent by the fifth to seventh day and which persists for ten days or more is a positive reaction. A negative reaction will show little more than a faint blush at this stage and will have faded completely within ten days. Negative skin tests occur in a small percentage of Brucella infections, as proved by positive culture. The significance of the positive cutaneous reaction is modified by the result of the opsonocytophagic test.

Phagocytic Index: The opsonocytophagic test must be performed promptly after the collection of 5.0 cubic centimeters of blood, accurately measured into a vial containing 0.2 of a cubic centimeter of 20 per cent sodium citrate in normal physiologic saline solution. Every

hour that this specimen stands progressively reduces the phagocytic power of the white cells. Technique must be highly accurate. If a non-virulent culture of Brucella is used, phagocytic power of the white cells is relatively increased and the result proportionately inaccurate. The number of live bacteria ingested by each of 25 polymorphonuclear leukocytes gives the direct index of the patient's resistance to Brucella infection. In general, a low or moderate degree of resistance, coupled with a positive cutaneous reaction in a patient with symptoms suggesting brucellosis, points to an infection from which the patient has not recovered.

A high degree of resistance in the presence of a positive skin test is usually indicative of an old infection from which the patient has recovered. Of course, there are exceptions. A patient with a virulent infection may die of it even in the presence of 100 per cent of marked phagocytosis, as in the patient reported by Robinson. Presence of a focus of infection, such as salpingitis or cholecystitis, may prevent recovery regardless of the phagocytic power of the white cells. The test should never be construed as "positive" or "negative." Its only significance lies in the relative degree of resistance indicated.

Special Problems in Diagnosis

Arthritis: Arthritis is among the very special problems in any discussion of brucellosis, because it is a common manifestation of this illness and because it is rarely considered. Joint involvement in acute undulant fever was described by Hughes[4] in his monograph in 1897. In 1933 O'Donoghue[5] stated that Malta fever joint infections must be added to the legions calling for differential diagnosis of acute and subacute joint conditions. Simpson,[6] Hardy,[7] Goldfain[8] and others, have called attention to the occurrence of joint manifestations in chronic brucellosis. No one has sufficiently stressed the high incidence of arthritis of all types in brucellosis, nor the crying need for its recognition and treatment.

Two cases of arthritis will be described in some detail because they belong in the category of the supposedly incurable, progressive arthritides and because one has made a complete recovery and the other is in process of getting well. Both are progressive atrophic rheumatoid processes, one a classical Marie-Strumpel type. The degree of restoration of the hip joints in the first patient, following treatment of the

Brucella infection, is clearly illustrated. The radiographs of the second patient shows similar joint pathology. Her clinical course to date suggests that an equally complete joint restoration can be hoped for.

Case No. 1. The first patient is a young white male, aged 21 when he was first seen on 9 September 1941 in consultation with Dr. Edward Hartung at Post-Graduate Hospital. He had been bedridden for a year because of bilateral involvement of knees, hips, sacro-iliac joints and of the right shoulder, in an atrophic-arthritic process which had begun in 1935. It had been steadily progressive. Hip joints were approaching ankylosis. Fever had ranged from 99°F. to 100°F. daily, with a high point of 102°F. Tachycardia and lassitude had been present throughout. Sedimentation rate had been consistently elevated, ranging from 28 millimeters to 55 millimeters per hour. There had been a loss of 30 pounds in weight. He had had the advantage of the most expert diagnostic and therapeutic measures currently available. Vitamin D in massive doses, weekly blood transfusions, gold salts, irradiation of auto-transfused blood, streptococcus vaccine, salicylates, iodine and thiamine chloride parenterally, hydrotherapy, diathermy, and finally roentgen therapy had all been given adequate trial with little or only temporary improvement.

Brucellosis was considered as a possible etiologic factor because: 1) Many cases of arthritis, of all types, apparently attributable to Brucella infection, had previously been seen; 2) A significant percentage of these patients had responded to specific Brucella vaccine; 3) The patient gave a history of consumption of raw milk from a herd of cattle subsequently shown to be infected, from 1926 to 1940; 4) All other possibilities of successful treatment apparently had been exhausted; 5) Experience over a period of nearly ten years had demonstrated that brucellosis must be considered in the diagnosis of any obscure illness. Blood agglutination test was negative, intradermal test was weakly positive on the fifth day; the visible, palpable, nodule persisted for more than twenty days, leaving little doubt of the significance of the reaction. The opsonocytophagic test indicated only slight resistance to Brucella infection, with marked phagocytosis in 2 cells, moderate in 3, slight in 9 and none in 11.

A therapeutic trial of Brucella abortus vaccine was begun on 29 September 1941. Physical therapy, consisting of massage, manipulation and hydrotherapy, was continued. Within three weeks of the initiation

Fig. 1.—Case 1. Marie-Strumpel type of rheumatoid arthritis, 20 March 1941, 3 years after onset.

of vaccine treatment, improvement was noted, especially in the hip joints. On 20 October 1941 the patient was able to sit on the edge of the bed for an hour. Fever steadily lessened. Sedimentation rate did not consistently parallel improvement. By 15 November 1941, seven weeks following the inception of Brucella vaccine therapy, the patient was walking with the aid of crutches. The left hip was still fixed in exten-

Fig. 2—Case 1. Further progression, 13 August 1941.

sion. The phagocytic index showed a steady increase (12-11-2-0 on 15 November 1941 and 16-9-0-0 on 6 December 1941). He left the hospital shortly thereafter. The vaccine was continued, with no local or general reaction at any time. By December 1942, 15 months later, he had sufficiently recovered to take a full-time job in a defense plant where he has been steadily employed since. Vaccine treatment was dis-

Fig. 3.—Case 1. Beginning reversal of process, 6 December 1941, 3 months following initiation of Brucella abortus vaccine therapy.

continud in March 1944 and reinstituted in August 1944 following two attack of iritis, involving both eyes separately, attributed to brucellosis by his attending ophthalmologist.

Review of x-ray findings revealed that definite x-ray changes had first been noted in March 1936, when the left sacro-iliac joint had showed chronic productive arthritis. In March 1938 both sacro-iliac

Fig. 4.—Case 1. Marked restoration of hip joints, 2 July 1942, 10 months following initiation of vaccine therapy.

joints were about equally involved with no demonstrable involvement of hip joints. In November 1939 there was "considerable condensing osteitis about both sacro-iliac joints, with generalized decalcification of pelvis and spine, and little involvement of the posterior intervertebral joints, characteristic of Marie-Strumpel arthritis." From that time on serial radiographs had showed progressive involvement of the hip joints

and finally obliteration of the sacro-iliac synchondroses. The first visual evidence of reversal of this supposedly irreversible process was noted in films made in December 1941, three months after the inception of specific vaccine therapy. Films made in July 1942 showed almost complete restoration of hip joints.

Case No. 2: This 19 year old girl was first examined by the writer in February 1944 in consultation with Dr. Andrew Campbell on the service of Dr. W. H. Irish at Post-Graduate Hospital. She had been well until ten years previously when there was a rather sudden onset of illness with chill and fever reaching 104°F., accompanied by a generalized rash, painful joints, headaches and prostration. The illness subsided after several weeks. She remained well for about a month after which all her symptoms returned for a period of six weeks. A diagnosis of rheumatic fever was made. Following recovery from this episode she began to have increasing difficulty in walking, with pain in both hips and stiffness of the knees. She had several recurrences of fever and rash and exacerbation of joint involvement and was twice hospitalized for several weeks prior to February 1936, first at Beekman Street Hospital and then at Presbyterian Hospital. During one attack the rash was thought to be scarlet fever. In October 1937 she was admitted to Welfare Island Hospital during another recurrence. Treatment had been continuous at out-patient clinics. She was admitted to Post-Graduate Hospital in April 1939 for treatment of her painful, stiff hips and knees, with a diagnosis of Still's disease, and was discharged to the outpatient department in May 1940, unimproved after physical therapy, Sutter fasciotomy, casts, manipulation and the like. She was repeatedly readmitted for manipulation to Post-Graduate Hospital between 1940 and 1943, with no clinical or radiographic evidence of improvement. Sedimentation rate was never over 36 millimeters per hour; blood counts were essentially normal except for relative lymphocytosis. Fever ranged from 97.6 to 101°F. for periods of from four to six weeks, with intervals of from six to eight weeks, with a daily sharp rise and sharp drop.

Following readmission to Post-Graduate Hospital in March 1943 for physical therapy and manipulation under anesthesia, she developed severe headaches and recurrence of fever which persisted for six weeks. Dr. Campbell, the resident physician, then suspected the inadequacy of the diagnosis of Still's disease. He recalled that she had lived on a farm

and had drunk raw milk prior to the onset of her illness. Blood culture for Brucella was negative, as was the blood agglutination reaction. Intradermal test gave an atypical positive reading. Phagocytic index was reported as "negative" (meaning, no doubt, that there was little or no phagocytic activity of the white cells). A therapeutic trial of a commercial Brucella vaccine was begun on 16 December 1943. Improvement began within a few days following the skin-testing dose of vaccine, was clinically noticeable within two weeks and has continued. She was able to walk without assistance within three months. Hip joints regained about 60 per cent of normal motion as compared with 30 per cent of normal range previously. Knee joints improved to about 40 per cent of normal range, from 10 per cent. Phagocytic indices done serially indicated marked coincidental increase in specific resistance. Temperature steadily returned toward normal during vaccine therapy. In view of this splendid progress made under the mixed vaccine regime, I did not advise use of the usually preferable Brucella abortus vaccine. In July 1944 there was another febrile episode with temperature to 101°F. and intense headache. During four days of sulfadiazine therapy toxic symptoms developed but temperature became normal, the fever recurring 24 hours after the drug was stopped. Penicillin was given to a total dosage of 500,000 units but with no effect on fever or headache. Brucella vaccine was then resumed, but with larger doses (2 cubic centimeters three times weekly). Within a week temperature subsided to normal and has remained so for the past 2½ months. Re-x-ray in June 1944 showed no change as compared with previous films.

The actual percentage of all arthritis caused by Brucella infection is not determinable. In rural regions, such as in the studies by Goldfain,[8] wherein arthritic patients have been life-long consumers of raw milk, it is to be expected that the percentage of Brucella arthritis will be higher than in a metropolitan region. Goldfain found that 51 per cent of 157 patients with arthritis also had chronic brucellosis; improvement "from moderate to marked degree and apparent cure occurred in a total of approximately 90 per cent of 23 cases adequately treated with Brucella bacterin." These patients all drank raw milk. I have repeatedly pointed out that the availability of pasteurized milk in large urban centers is not sufficient guarantee that their inhabitants may not be exposed to Brucella infection. The two obvious sources of infection of urban dwellers are raw milk consumed during vacations in the country,

or raw milk in childhood, or *certified* raw milk. Until recent months all certified milk in this region was raw. Finally, apparently as a result of various exposés of the presence of Brucella organisms in certified raw milk, one of the leading producers of certified milk has conducted an advertising campaign introducing *certified pasteurized* milk. On the basis of my own civilian practice among both rural and urban dwellers I would hazard the guess that perhaps 5 to 10 per cent of all arthritis is due to Brucella infection. Unfortunately, it has to remain a pure guess until some one, specializing in arthritis, will carefully study every patient encountered, for Brucella infection as well as for other etiologic factors. To determine the blood agglutination reaction only and to omit the most careful use of the multiple tests will give a false picture since the majority of patients with chronic brucellosis show no agglutinins in their blood, or in low titer only.

It will not be an accurate study unless patients representing a cross-section of the population of the United States are included—farmers, dairy workers, butchers, slaughterhouse employees, laboratory workers, rural and urban dwellers. It should be correlated with the history of ingestion of raw milk or its products, and of contact with cattle, at any time in these patients' lives. The infection may remain latent or sub-clinical for any number of years, apparently being lighted up in some patients by unusual fatigue, intercurrent illness or even by slight trauma.

Of my series of 427 patients with brucellosis, about equally divided between rural and urban dwellers, there were 74 (17.3 per cent) with atrophic or hypertrophic arthritis. Patients were not included whose arthritis may have been coincidental only. The evaluation was made on the basis of clinical study plus response to specific vaccine therapy. Cases seen in the naval service were not included. Cultural study of synovial fluid or blood was not usually undertaken because of the difficulty in persuading well-trained laboratory personnel of its importance and of the need to use the special cultural procedures for the isolation of Brucella.

Salpingitis: Of the vast number of other frequent or important localizations of Brucella infection time allows of discussion of but a few. Salpingitis is chosen for special mention because of its frequent occurrence in Brucella infection, its infrequent recognition, and its importance, especially in the childbearing age. Cystitis and pyelitis, along

with salpingitis, endocervicitis, endometritis, ovarian cysts and abscesses, will only be mentioned as sites of Brucella infection of the genito-urinary tract, frequently occurring but usually attributed to other organisms.

Clinically, salpingitis due to Brucella infection differs from that of other origin in two important respects–its tendency to remain subclinical in many patients and its tendency to undergo spontaneous regression with frequent exacerbations. In the patient referred to elsewhere whose three abortions were followed by isolation of the organism, a most competent gynecologist reported negative pelvic findings within a week of the time that I had found the right tube markedly distended and tender. Ten days following this negative report there was recurrence of right lower quadrant pain and tenderness, low grade fever and malaise. Culture made diagnosis positive. In the absence of any attempt at or interest in cultural proof it is easy for the gynecologist to take refuge in such negative comments as, "I have never encountered a tubal infection caused by Brucella" or, "To the best of my knowledge most cases of salpingitis are still produced by a vicious little organism, first described by Neisser." Adequate cultural study in a large series of tubal infections still remains to be done.

Until such a study is undertaken the only data available must be furnished by isolated definitive cases of female genital infection, such as the one reported by me, and by various others, and by clinical evidence of its relative frequency. Among 192 female patients with brucellosis between the ages of 18 and 45, I found 24 cases of salpingitis (12.4 per cent) of apparently non-venereal origin. Only one yielded positive culture for Brucella. Few had the advantage of cultural study however. Gonococcal infection was excluded, as nearly as possible, by blood complement fixation tests, cultures and smears. The clinical diagnosis of brucellosis was arrived at by use of the blood agglutination reaction, intradermal test and determination of the phagocytic index, plus characteristic response to therapeutic test doses of Brucella abortus vaccine. Five patients had exploratory laparotomies with no competent cultural examination of the operative specimens.

Treatment

The Acute Illness: The acutely ill patient must have bed-rest because of the usual prostration, sweating, fever and various complications

such as joint involvement, respiratory tract infection, and the like. General supportive measures are, of course, indicated. Sulfathiazole, sulfadiazine, or sulfamerazine offer a way of bringing about remission but probably usually not of actual cure. Response to the sulfonamide compounds is usually noted within 48 hours or less. Two common errors are made in the use of sulfonamide compounds. The first is use of an insufficient daily dose and the second is its discontinuance after only two or three days of normal temperature range. Fairly full dosage (one gram six times daily for 2 or 3 days, then one gram four times daily) is indicated until temperature has remained normal for three or more days, following which dosage may be reduced to a half gram four or even three times daily, for two or three weeks longer.

It is wise to begin vaccine treatment about two weeks before discontinuance of the sulfonamide compound unless a very high degree of phagocytic activity already is present as the result of natural defense reactions. This is to guard against preventable relapse. If, during convalescence, a rising phagocytic index is found on frequent serial tests, and if it remains high for a period of months after apparent complete recovery, vaccine treatment is unnecessary at least at that time. A certain unknown percentage of acutely ill patients may have but one acute attack, with no subsequent acute exacerbations. Others develop chronic illness, too often confused with protracted convalescence. Unless their white cells possess adequate phagocytic activity, relapse must be considered likely and active measures taken for its prevention. It is my practice to repeat the determination of the phagocytic power of the white cells, at weekly intervals until the index has reached a satisfactory level and then biweekly or monthly, throughout active treatment. After discontinuance of vaccine therapy, the patient may be granted longer and longer respites from observation until a minimum of two years has elapsed in the absence of symptoms. Recrudescence of any symptoms possibly referable to brucellosis is an indication for repetition of the test, at any time. Relapse will rarely occur under this seemingly overly zealous regime. A significant fall in two successive tests must not be ignored since impending relapse is thereby almost invariably predictable, in the absence of actual cure.

In patients whose sensitivity to sulfonamide compounds cannot be overcome, or in those resistant to their effects, expectant treatment is justified only if the patient's general condition is excellent. The average

acute illness may terminate itself within three to five weeks or it may last eight to twelve weeks or longer. The mortality of about 2 per cent is not negligible, and it may be much higher in virulent outbreaks. In one such epidemic of Brucella suis origin a mortality of 25 per cent occurred. Development of irreversible processes such as Brucella endocarditis, not rarely reported, furnishes additional reasons for attempting to bring about remission as soon as possible. Use of Foshay's immune serum is usually effective in bringing about remissions in cases of less than four months duration, as may be transfusions of immune blood. Fever therapy may be successful in some. Huddleson[9] no longer advises the use of his filtrate of the mixed strains of Brucella in the presence of fever of 103°F. or higher, nor is the use of any vaccine indicated at this stage, ordinarily. Foshay's detoxified (nitrous acid treated) Brucella abortus vaccine may be used in very dilute, reactionless doses when other measures fail and the febrile course is prolonged, however.

The Chronic Illness: The first problem is to determine the degree of resistance already attained by the patient's white cells. If the opsonocytophagic test has recently been done in the course of the diagnostic study, that information is already available. Occasionally active infection persists even in the presence of a high phagocytic index. The organism may localize in any tissue in the body as shown by positive culture in living patients and post mortem. In general the patient with a low or moderate level of phagocytic activity, in the presence of clinical symptoms probably referable to brucellosis, should have the benefit of active specific therapy.

Vaccine therapy remains the method of choice for the initiation of treatment in the chronic infection. Recovery is brought about in approximately 75 per cent of cases, with marked improvement in an additional 15 to 20 per cent, under circumstances that leave no doubt as to its specificity. Recovery cannot be attributed to the non-specific effect of Brucella vaccine. If indeed one is so bold as to say it can be so attributed, then there must be in Brucella vaccine a most remarkable foreign protein of which the profession has remained ignorant. Phagocytic indices will almost invariably parallel the clinical course of the patient under treatment, rising as improvement occurs and falling in advance of or concurrent with relapse. A persistently high level of phagocytic activity is found in those who make uneventful recoveries and who remain well.

The type of vaccine is of importance. With Calder and others, I believe that the use of vaccine made from the abortus strain alone will result in less reaction, more prompt and lasting response, and a larger percentage of recoveries than from the use of vaccines of mixed strains of abortus and suis, or abortus and melitensis. There are, however, notable exceptions, as in Case 2 quoted above where a commercial mixed vaccine was used with such excellent early results. In this patient another exception was noted in that much larger and much more frequent dosage than average was necessary in re-establishing the course toward recovery.

The vaccine employed in nearly all of my 427 cases was prepared by the New York State Department of Health from a heat-killed strain of Brucella abortus isolated from the blood of a human patient. Reactions are kept to a minimum by use of whatever dilution is necessary, with the aim of desensitization by gradual increase in number of organisms. Phagocytic response seems best stimulated in this manner. There has been no similar vaccine commercially available except on special order. One of the leading makers of biologicals is in the process of marketing such a vaccine, however, and promises its availability by January 1945.

It is essential to vary the route, interval, dilution and dosage with the needs of the patient. In the vast majority the intramuscular route is preferable. In a small percentage intradermal administration, with or without concomitant intramuscular administration, produces more satisfactory increase in opsonic power of the white cells. In those who fail to achieve a high level of resistance, the intravenous use of the vaccine is indicated and usually is very effective. The optimum interval is that which produces the least reaction, the greatest sense of well-being, and the most marked phagocytic response. This varies from four to seven days but occasionally should be as short as two or three days. Dosage and dilution employed should be that which produces minimal reactions, with small increments. The dilutions usually needed are 1:10, 1:100 or 1:1000. The duration of treatment depends entirely on clinical and serologic response and tendency to relapse.

Treatment of Localized Infections: Discussion will be confined to arthritis and salpingitis, although infections of the gallbladder, prostate, urinary tract and other localizations are equally important when encountered.

Arthritis may not yield to Brucella vaccine therapy alone but recovery, especially in the presence of extensive damage, may be hastened or made more complete by judicious use of diathermy for the involved joint or joints, or, in some instances, by fever therapy. Spondylitis seems to yield better to fever therapy than do other complications of brucellosis, in the opinion of Phalen, Prickman and Krusen[10] of the Mayo Clinic. They quoted the earlier observation made by Thompson, Sheard and Larson who remarked that fever therapy is of value apparently through activating or heightening of the intrinsic mechanisms of the body rather than by bactericidal effect. They took cognizance of the fact that Brucella abortus organisms can survive 107°F. for 24 hours in vitro. Their patients apparently had not had the benefit of adequate trial of Brucella vaccine however. I believe, with Simpson,[6] that fever therapy should be reserved for those patients who fail to respond to vaccine.

Salpingitis often will not yield to vaccine treatment alone. In fact the presence of this localized infection will frequently prevent recovery from the systemic infection, apparently serving as a persistent focus of infection until local treatment is added to the vaccine regime. In such instances ultrashort wave diathermy, using the Bierman or Gottesman vaginal electrode, in a majority of cases, will result in clinical cure of the tubal infection, which is usually then followed by complete recovery. High local temperatures and prolonged treatments are necessary. Surgical removal does not necessarily accomplish cure. Too many tubes and ovaries already have been sacrificed, as was formerly true in gonorrheal infections, not to re-emphasize this point vigorously. The infection itself produces so great a number of cases of sterility through tubal infections and abortions that every conservative means should be utilized to avoid the certainty of sterility through needless sacrifice of tubes and ovaries.

Vitamin B Complex probably plays a role in the recovery from the chronic infection through its recognized ability to increase the phagocytic power of the white cells. Its use should be routine, I believe, not only during active treatment but for a long period thereafter. Other useful measures in the chronic illness include the sulfonamide compounds in a small proportion of patients, Foshay's detoxified vaccine, and fever therapy in those cases refractory to vaccine therapy.

There still seems to be some reason to hope that penicillin or other

mold derivatives such as streptothrycin or streptomycin will prove to be bactericidal agents. The early work of Walter Kochalaty[11] at the University of Pennsylvania gave encouragement to the belief that penatin would be effective in human infections. However, he was unable to reproduce his earlier favorable findings. The early literature on penicillin has yielded only negative evidence of its value, with one noteworthy exception. Tsun T'ung,[12] reporting his observations on the in vitro action of penicillin alone and in combination with sulfathiazole, stated that certain strains of Brucella had proved to be susceptible to penicillin, and that the effect was enhanced by sodium sulfathiazole. No clinical application of his idea has come to my attention. H. F. Flippen[13] of Philadelphia has used the material in several patients with arthritis whose agglutination tests were positive with no striking results, but in no case of brucellosis with a positive culture. Andrew Campbell[14] administered 500,000 units of penicillin to the patient described as Case 2 in the midst of a febrile relapse but with no improvement.

Comment

Many problems difficult of solution are encountered in the diagnosis and treatment of brucellosis. The major ones consist of the lack of a single uniformly definitive diagnostic measure, the failure to use and to correctly interpret the multiple tests, the tendency of brucellosis to simulate numerous other diseases, and the present lack of any truly bactericidal chemotherapeutic agent. However, not the least of the problems are caused by the emotional states precipitated by (and in turn aggravating and perhaps preventing recovery from) this debilitating and often frustrating disease. The patient's unwillingness to abandon the solid ground furnished by an earlier diagnosis of a somatic illness for what they consider to be the less tangible and more onerous diagnosis of neurosis, adds to an already complicated problem. As physicians, our own understanding of the mechanism of psychosomatic conditions is too incomplete to expect patients to accept readily our concepts of the psychic and somatic components of disease and to coöperate in the psychotherapy of the psychogenic, along with specific therapy of the infectious process when indicated. Intelligent management of both components are vital to success in some of these patients, however.

Summary

The role of Brucella infection in the etiology of various common infectious processes, along with diagnostic and treatment problems, is discussed.*

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* Opinions expressed are those of the author and do not necessarily reflect those of the Medical Department of the Navy or of the naval service at large.

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